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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/727,770	12/04/2000	Znenya Li	CL000651	5477

25748 7590 07/22/2004

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/727,770	LI ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,9 and 24-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8,9 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/20/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 20 May 2004 in reply to the Non-Final Office Action mailed 20 November 2003. Claims 4, 8, 9 and 24-29 were considered in the 20 November Office Action. Claim 9 was amended in the 20 May Paper. Claims 4, 8, 9 and 24-29 are pending and under consideration.

Response to Amendment

Claim Objections

Objection to claim 9 as encompassing nonelected subject matter is withdrawn in view of the amendment thereof.

Response to Arguments

Claim Rejections - 35 USC § 101 and 112, first paragraph

Claims 4, 8, 9 and 24-29 stand rejected under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Before addressing Applicant's arguments, it should be made clear that the claims have been rejected because they are not supported by a specific and substantial asserted utility or a well-established utility, not because the asserted utilities have been deemed incredible.

It should also be made clear that a "specific utility" is *specific* to the subject matter claimed, in contrast with a *general* utility that would be applicable to the broad class of the

invention, and "substantial utility" is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Further, a "well-established utility" is a specific, substantial and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material alone or taken with the knowledge of one skilled in the art.

In response to the *prima facie* case and arguments of record, applicant first traverses the Examiner's assertion that the evidence of record does not establish that the claimed invention has the function of a vacuolar ATP synthase as asserted in the application. While acknowledging an insect vacuolar ATP synthase subunit C may be more closely related to the human vacuolar ATP synthase than the instant polypeptide, Applicant questions how this relationship brings into question the identification of the instant polypeptide as a vacuolar ATP synthase.

By way of clarification, the statement referred to by Applicant was made in the 24 February 2003 Office Action and reads as follows, "[the data cited] shows that proteins having the function of a ATP synthase 16 kDa proteolipid subunit are highly conserved among mammals, and that even the insect ATP synthase 16 kDa proteolipid subunit is more closely related to the human ATP synthase 16 kDa proteolipid subunit than the instant polypeptide" (page 5). The point of this statement is that structural conservation within the family of proteins established to function as ATP synthase 16 kDa proteolipid subunits within mammals is extremely high (greater than 90% across human, ovine, bovine and mouse). It was pointed out that the insect ATP synthase 16 kDa proteolipid subunit is more closely related to the human ATP synthase 16 kDa proteolipid subunit than the instant polypeptide merely to illustrate that the

structural similarity of the claimed protein to proteins established to function as an ATP synthase 16 kDa proteolipid subunit is substantially less than the structural conservation that is typical of proteins having that function. Given that even small changes in protein structure can produce significant changes in function, the skilled artisan would expect that the structural divergence of the claimed protein from proteins having established function would have some functional significance. Thus, even if the claimed invention did have some function in common with an ATP synthase subunit C, which is not established by the data presented in the specification, it is highly likely that it has other functions that are distinct from those of known ATP synthase subunits C. As the disclosure does not identify which functions of an ATP synthase are comprised by the polypeptide encoded by the claimed invention and provides no explanation of how the distinct structural characteristics of the claimed invention affect its function, the skilled artisan simply does not know what the specific functional characteristics of the claimed invention would be; therefore, the specification fails to provide a disclosure of the specific functional characteristics of the claimed invention such that the utility of the invention would be immediately apparent to the skilled artisan.

Next, Applicant points out that the Hummer search result shows that the protein of the present invention has a statistically significant domain of ATP synthase subunit C, not just an ATPase domain, and that the present invention has 52% homology with tomato vacuolar proton translocating ATPase, which Applicant alleges to support that, even at this low homology, the vacuolar ATP synthase domain is highly conserved.

This argument has been fully considered but is not deemed persuasive because the data presented do not establish the specific function of the claimed invention. First, the Hummer data

are presented in the specification with no explanation as to their significance. Does every polypeptide for which an Hmmer search returns a score of 14.8 and a description of "ATP synthase subunit C" have a specific and substantial utility? What is the meaning of the parsed data? The score for domain 2 is almost twice as high as the score for domain 1. Does this mean that the protein is more likely to have the domain 2 function? If so, do all proteins that have domain 2 function have a specific and substantial utility even in the absence of domain 1? It is impossible for one of ordinary skill to know the answers to these questions because essential information (*e.g.*, the functional properties of domains 1 and 2) is missing from the specification. In spite of the absence of any meaningful explanation of the Hmmer search results in the disclosure, Applicant relies heavily on these data to establish the functional properties of the claimed invention. Clearly, however, these data do not adequately inform the skilled artisan of the specific functional characteristics of the claimed invention.

With regard to the data presented showing 52% homology with a tomato vacuolar proton translocating ATPase, it is unclear how Applicant has arrived at the conclusion that the vacuolar ATP synthase domain is highly conserved. Exhibit 1 shows only 52% identity over 139 amino acids. Applicant does not specifically identify any region in the tomato vacuolar proton translocating ATPase sequence as "the vacuolar ATP synthase domain", or a region of particularly high sequence identity that would lead one to conclude that there is a conserved functional domain. In fact, the sequence alignment provided in the Exhibit is misformatted so that, even if there are regions of relatively high sequence identity, they are not apparent from the data provided. Furthermore, even if one could establish unequivocally that the claimed invention comprised a vacuolar ATP synthase domain, the specification does not provide a specific and

substantial utility common to all proteins that comprise such a domain. Given that the claimed invention has only 52% identity with a tomato vacuolar proton translocating ATPase, one of ordinary skill would expect the protein to have functional characteristics that are distinct from those of the a tomato vacuolar proton translocating ATPase. Again, as the disclosure does not identify which functions of an ATP synthase are comprised by the polypeptide encoded by the claimed invention and provides no explanation of how the distinct structural characteristics of the claimed invention affect its function, the skilled artisan simply does not know what the specific functional characteristics of the claimed invention are and, therefore, the utility of the invention would not be immediately apparent to the skilled artisan.

In support of an asserted "real-world" utility, Applicant cites teachings from the specification that differential regulation of H^+-K^+-ATPases takes place in acid-base and electrolyte disorders and that both the H^+-K^+-ATPase and the claimed protein are expressed in the kidney and that the colonic H^+-K^+-ATPase shows adaptive regulation in pathophysiological conditions such as K^+ depletion, NaCl deficiency, and proximal renal tubular acidosis, suggesting an important role for this exchanger in potassium, HCO_3, and sodium (or chloride) reabsoption in disease states such as polycystic kidney disease. By this, it is presumed that Applicant is alleging that the specification specifically identifies conditions such as K^+ depletion, NaCl deficiency, and proximal renal tubular acidosis as targets for diagnosis or intervention according to the teachings in the specification. On the contrary, the teachings amount to no more than speculation which appears to be based on the proximity of the claimed invention to an H^+-K^+-ATPase. This is not a specific and substantial asserted utility; rather, it is a hypothesis to be tested.

Likewise, the teachings from the art cited by Applicant which indicate vacuolar ATP synthases function in cellular and physiological processes; are expressed on the plasma membrane of human tumor cells; are involved in renal acidification; and function in bone resorption do not amount to a well-established specific and substantial utility. Although it is reasonable to expect that the claimed invention functions in cellular and physiological processes, the same is true of all naturally occurring proteins and therefore a teaching that a protein is likely involved in cellular and physiological processes does not constitute a specific or substantial utility. Furthermore, the disclosure does not establish that the particular protein encoded by the claimed nucleic acid is expressed on the plasma membrane of human tumor cells, is involved in renal acidification or functions in bone resorption; thus, even if some vacuolar ATP synthases have the recited properties, there is no evidence that the protein at issue has any of these properties. The claimed protein is indisputably different from all vacuolar ATP synthase subunits C known in the art at the time of filing; therefore, the assertion that the instant protein is expressed on the plasma membrane of human tumor cells, is involved in renal acidification or functions in bone resorption is merely speculation based on teachings that proteins having some limited structural similarity with the claimed invention have these properties. This does not amount to a disclosure of a utility specific to the claimed invention and it would clearly require additional experimentation to reasonably confirm that the claimed invention had any of the properties disclosed in the cited art.

Furthermore, even if one were to assume, *arguendo*, that the claimed protein is expressed on the plasma membrane of human tumor cells like the protein of Martinez-Zaguilan *et al.*, is involved in renal acidification like the protein of Brown *et al.* or functions in bone resorption like

the protein of Chatterjee *et al.*, there is no specific utility that universally applies to all proteins having these properties and there is no basis in the disclosure for a specific and substantial utility for a protein having these properties. One of ordinary skill in the art does not know how to use a protein that is expressed on a human tumor cell unless that expression is established to be a viable diagnostic marker or target for anticancer therapy. One does not know how to use a protein involved in renal acidification or bone resorption unless it is known how the protein is involved in the process and how modifying the function or expression of the protein affects the process. Thus, not only does the specification fail to establish that the claimed invention has the properties of the proteins in the cited art, it fails to provide a specific and substantial teaching of how any protein having those properties can be used.

In response to the Examiner's comments regarding the case of *Nelson v. Bowler*, Applicant alleges that the facts in the instant case are indeed analogous to those of *Nelson v. Bowler* and asserts that according to *Nelson*, not establishing a specific therapeutic use does not preclude a practical utility. Applicant states, "[l]ike *Nelson*, which states that 'knowledge of the pharmacological activity of any compound is obviously beneficial to the public,' the knowledge that the polypeptide of the instant invention is a vacuolar ATP synthase brings benefit to the public." In subsequent discussion Applicant further argues, "by placing a new member of the transporter protein family into the public domain through the patenting process, the present invention is not only a clear advancement over the prior art (a newly discovered protein/gene) but also enables significant advancement in medicine and further discovery" and "[t]he grant of a patent to the claimed isolated nucleic acid molecule and the resultant disclosure of the nucleic

acid and protein sequences to the public will certainly shorten the process for medical researchers to discover other novel uses for the present transporter-encoding nucleic acids."

First, regarding *Nelson*, as pointed out in the previous Office Action, the CCPA found that the pharmacological activity demonstrated by Nelson was sufficient to satisfy the utility requirement of 35 U.S.C. §101. However, in the instant case, no pharmacological activity has been demonstrated. Applicant merely speculates that, because the claimed nucleic acid encodes a naturally occurring protein and proteins are frequently targets of therapeutic agents, the polypeptide encoded by the claimed nucleic acid must also be a target of therapeutic agents. For reasons of record, applicant has failed to establish the specific functional properties of the claimed invention such that a specific and substantial utility would be readily apparent to one of ordinary skill in the art, and fails to provide anything more than general assertions of utility in the specification.

With regard to benefit to the public, similar issues were addressed by the Supreme Court in *Brenner v. Manson*, 148 USPQ 689 (1966). In *Brenner v. Manson*, the court concluded that "[t]he basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field" (*Id.* at page 695). Applicant's argument that the disclosure of the claimed invention itself provides immediate benefit to the public was also addressed by the Court in *Brenner v. Manson*. The Court noted that, while there is value in encouraging disclosure, "a more compelling consideration is that a process patent in the chemical field, which

has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public" (*Id.* at page 695). Likewise, in the absence of a specific and substantial utility for the instant claimed nucleic acid, the grant of patent rights which may engross a vast, unknown, and perhaps unknowable area is not clearly commanded by the statute.

Finally, in response to the Examiner's contention that developing reagents that can be used to investigate the properties of the claimed invention or treat unspecified diseases is neither a specific nor substantial utility, Applicant argues that "[s]ince the protein encoded by the instant invention is a vacuolar ATP synthase, reagents specific for the instant invention would have a specific and substantial utility" (page 10). However, for reasons of record, the instant disclosure fails to establish that the polypeptide encoded by the claimed nucleic acid is an ATP synthase, fails teach the unique properties of the claimed invention, and fails to teach a specific "real-world" utility for the claimed nucleic acid. As stated in the previous Office Action, "[a] teaching of specific utility requires more than a general statement that a specific utility is likely to exist by virtue of the invention being different from other molecules belonging to the same class. Instead, the specific utility must actually be contemplated by the inventor" (20 November Office Action, page 10).

Applicant's arguments have been fully considered but are not deemed persuasive either individually or as a whole. The *prima facie* case and arguments of record clearly establish that the specification fails to assert a specific and substantial utility or disclose of the properties of the claimed invention such that a well-established utility would be apparent to one of ordinary skill in the art; therefore, the claims fail to meet the requirements of 35 U.S.C. §101 and 112, first paragraph.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

DAVID GUZO
PRIMARY EXAMINER